REMARKS

Following entry of the foregoing amendments, claims 1, 2, 6, 7, 27, and 31 to 36 will be pending in the application. Claims 1, 2, and 27 have been amended, herein. No claims have been canceled, and no new claims have been added. Support for the amendments is found throughout the specification as originally filed, including, for example, paragraphs 91 to 93.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

A. Claims 1, 2, 6, and 27 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Sugimura *et al. Melanoma Res.,* 1992, 2, 191-196 ("the Sugimura reference") in view of U.S. Patent No. 5,804,183 ("the Filpula patent") and O'Brien, W.E., *Biochemistry*, 1979, 18(24), 5353-5356 ("the O'Brien reference"). Applicants respectfully request reconsideration and withdrawal of the rejection because the cited references, when considered individually or in combination, fail to teach or suggest all the limitations of the present claims.

Preliminarily, Applicants note that claim 1 has been amended to recite methods for identifying cancer patients suffering from hepatoma or sarcoma who are susceptible to arginine deprivation therapy that comprising detecting the presence or absence of argininosuccinate synthetase protein in hepatoma or sarcoma samples from the patients.[1]

Such methods would not have been obvious to those of ordinary skill in the art at the time of the invention because, prior to Applicants' efforts, it had not been recognized or appreciated in the art that the level of argininosuccinate synthetase protein expressed in hepatoma or sarcoma cells could be used to predict whether the hepatomas and sarcomas would be sensitive to arginine deprivation therapy. The art did not teach or suggest that the level of argininosuccinate synthetase protein in a hepatoma or sarcoma tumor sample could

[1] Claims 2 and 27 have been amended consistent with amended claim 1.

be used to determine whether the patient from which the sample was obtained was a candidate for arginine deprivation therapy.

The Sugimura reference describes experiments in which the sensitivity of five human melanoma cell lines and one human carcinoma cell line to *Mycoplasma arginini* arginine deiminase was determined. The reported results indicate that the growth of cells of each of the melanoma cell lines was inhibited by arginine deiminase, although to varying degrees, but the growth of the carcinoma cells was not affected. Proliferation of the C32TG, Mewo, and VMRG-MELG melanoma cells was inhibited by 16 ng/ml of arginine deiminase, and proliferation of the A375 melanoma cells was almost completely inhibited by 32 ng/ml of arginine deiminase.[2] The melanoma cell line G361 "also exhibited high sensitivity to AD, showing a marginal response (23% of control cell proliferation) at 130 ng/ml of AD."[3] In contrast, "[t]he growth of HeLa [carconima] cells was hardly affected by AD."[4] Further experiments were conducted to determine the level of argininosuccinate synthetase mRNA present in cells of each cell line, with the cell line TL-Mor serving as a positive control. Argininosuccinate synthetase transcripts were not detected in the C32TG, Mewo, and VMRC-MELG cells.[5] The level of argininosuccinate synthetase transcripts detected in A375 cells and G361 cells was 1/34 and 1/5, respectively, of that found in TL-Mor,[6] while the level of argininosuccinate synthetase transcripts in HeLa cells was 1/3 of that of TL-Mor.[7]

The level of argininosuccinate synthetase mRNA in the G361 melanoma cells was 20 % of that of the control cell line, but the G361 melanoma cells still exhibited "high sensitivity to AD."[8] In contrast, the level of argininosuccinate synthetase mRNA in the carcinoma cells was 33 % of that of the control cells, but the carcinoma cells were ***not*** sensitive to arginine deiminase. Thus, melanoma cells and carcinoma cells were shown to have similar levels of argininosuccinate synthetase mRNA, but very different degrees of sensitivity to arginine deiminase. Based upon these results, at the time of the invention, those skilled in the art would not have concluded that the level of argininosuccinate synthetase expression in cells of

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[2] Page 193, first column, first full paragraph.
[3] *Id.*
[4] *Id.*
[5] Page 194, paragraph bridging columns 1 and 2.
[6] *Id.*
[7] *Id.*
[8] Page 193, first column, first full paragraph.

different tumor types could have been used to successfully predict whether particular tumors would have been sensitive to arginine deiminase. The Sugimura reference, accordingly, does not suggest that argininosuccinate synthetase protein levels in a hepatoma or sarcoma sample derived from a cancer patient could be used to determine whether the patient would be a candidate for arginine deprivation therapy.

The remaining references do not compensate for the deficiencies of the Sugimura reference. The Filpula patent describes conjugation of *Mycoplasma arthritidis* arginine deiminase to polymers and teaches that the conjugates can be used to treat a variety of conditions known to respond to arginine deiminase deprivation therapy.[9] The patent states that such conditions include carcinomas that are deficient in argininosuccinate synthetase, such as the melanomas described by the Sugimura reference. The patent thus erroneously indicates that melanomas are a type of carcinoma, and, significantly, provides no independent evidence that arginine deiminase can be used to treat carcinomas, other than citing the Sugimura reference.

The Filpula patent thus teaches that *Mycoplasma arthritidis* arginine deiminase can be used to treat conditions that are known to respond to arginine deprivation, which include melanomas deficient in argininosuccinate synthetase. The patent does not independently report the level of argininosuccinate synthetase expression in carcinoma or melanoma cells, however, but cites the Sugimura reference for the proposition that melanoma cells are deficient in argininosuccinate synthetase. Moreover, the patent does not teach or suggest that levels of argininosuccinate synthetase expression in different tumor types can be used to predict the sensitivity of particular tumors to arginine deiminase therapy. The patent, accordingly, does not teach or suggest that argininosuccinate synthetase protein levels in hepatoma or sarcoma cells from cancer patients should be determined in order to ascertain whether the patients would be sensitive to arginine deiminase therapy.

Finally, the O'Brien reference describes the purification and characterization of argininosuccinate synthetase from human liver. The reference does not teach or suggest that levels of argininosuccinate synthetase expression in hepatoma or sarcoma cells can be used to predict the sensitivity of the cells to arginine deiminase therapy. The reference also does not

[9] Col. 13, lns. 6-15.

teach or suggest that argininosuccinate synthetase levels in hepatoma or sarcoma cells of cancer patients should be measured to determine whether the patients are candidates for arginine deiminase therapy.

When the Sugimura reference, the Filpula patent, and the O'Brien reference are combined, they fail to teach or suggest the claimed methods. The Sugimura reference teaches that the level of argininosuccinate synthetase mRNA present in cells of different cancer types does not correlate with the cells' sensitivity to arginine deiminase. The level of argininosuccinate synthetase mRNA in cells of the melanoma cell line G361 was 20 % of that of cells of the control cell line, but the G361 cells still exhibited high sensitivity to arginine deiminase. In contrast, the level of argininosuccinate synthetase mRNA in cells of the carcinoma cell line HeLa was 33 % of that of cells of the control cell line, but the carcinoma cells were completely insensitive to arginine deiminase. The Filpula patent teaches that polymer conjugates of arginine deiminase can be used to treat conditions known to respond to arginine deiminase therapy, such as melanoma as described in the Sugimura reference, but does not independently report the level of argininosuccinate synthetase expression in melanoma cells. The O'Brien reference describes the purification and characterization of argininosuccinate synthetase from human liver.

Accordingly, when the cited references are combined, they suggest that arginine deiminase may ***potentially*** be used to treat melanoma, due to the demonstration that such cells are sensitive to arginine deiminase. The references, however, ***do not*** teach or suggest that the level of argininosuccinate synthetase protein present in different types of tumor cells can be used to predict whether particular tumors will be sensitive to arginine deprivation therapy. Accordingly, the references fail to teach or suggest methods for identifying cancer patients suffering from hepatoma or sarcoma who are susceptible to arginine deprivation therapy that involve determining the level of argininosuccinate synthetase protein present in hepatoma or sarcoma samples from the patients. The claimed methods, therefore, would not have been obvious to those skilled in the art at the time of the invention. Applicants accordingly, respectfully, request withdrawal of the rejection.

Applicants note that the Office asserts that the Filpula patent describes the treatment of carcinoma deficient in argininosuccinate synthetase with arginine deiminase.[10] As discussed above, however, citing the Sugimura reference, the Filpula patent states that arginine deiminase conjugates may be used to treat carcinomas deficient in argininosuccinate synthetase, such as the melanomas described by the Sugimura reference. The patent thus erroneously states that melanomas are a type of carcinoma, and provides no actual evidence that arginine deiminase can be used to treat carcinomas. As also discussed above, the Sugimura reference indicates that the growth of carcinoma cells were not affected by arginine deiminase. The Office, accordingly, incorrectly asserts that the cited art teaches that carcinomas have been successfully treated with arginine deiminase, because the references contain no such teaching.

B. Claims 6, 7, 31, 32, 35, and 36 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Sugimura reference in view of the Filpula patent, the O'Brien reference, and U.S. Patent No. 5,424,192 ("the Thompson patent"). Applicants respectfully request reconsideration and withdrawal of the rejection because the cited references fail to teach or suggest every limitation of the cited claims. The teachings of the Sugimura reference, the Filpula patent, and the O'Brien reference are discussed above. The Thompson patent describes methods for detecting prostate cancer using an antibody labeled with a detectable label. The patent fails to teach or suggest that argininosuccinate synthetase levels in hepatoma or sarcoma cells of cancer patients should be measured to determine whether the patients are candidates for arginine deiminase therapy. Accordingly, for the reasons discussed above, the cited references, when considered individually or in combination, fail to teach or suggest methods for identifying cancer patients suffering from hepatoma or sarcoma who are susceptible to arginine deprivation therapy that involve determining the level of argininosuccinate synthetase protein present in hepatoma or sarcoma samples from the patients. Applicants accordingly, respectfully, request withdrawal of the rejection.

C. Claim 33 has been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Sugimura reference in view of the Filpula patent, the O'Brien reference, and U.S. Patent No. 6,068,830 ("the Diamandis patent"). Applicants respectfully request reconsideration and

[10] Office action dated July 31, 2006, page 6.

withdrawal of the rejection because the cited references fail to teach or suggest every limitation of the cited claims. The teachings of the Sugimura reference, the Filpula patent, and the O'Brien reference are discussed above. The Diamandis patent describes methods for imaging cancer using an antibody labeled with a radioisotope. The patent fails to teach or suggest that argininosuccinate synthetase levels in hepatoma or sarcoma cells of cancer patients should be measured to determine whether the patients are candidates for arginine deiminase therapy. Accordingly, for the reasons discussed above, the cited references, when considered individually or in combination, fail to teach or suggest methods for identifying cancer patients suffering from hepatoma or sarcoma who are susceptible to arginine deprivation therapy that involve determining the level of argininosuccinate synthetase protein present in hepatoma or sarcoma samples from the patients. Applicants accordingly, respectfully, request withdrawal of the rejection.

D. Claim 34 has been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Sugimura reference in view of the Filpula patent, the O'Brien reference, U.S. Patent No. 6,124,106 ("the Wallace patent"), and Hansen, *et al.*, *Electrophoresis*, 1989, 10(8-9), 645-652 ("the Hansen reference"). Applicants respectfully request reconsideration and withdrawal of the rejection because the cited references fail to teach or suggest every limitation of the cited claims. The teachings of the Sugimura reference, the Filpula patent, and the O'Brien reference are discussed above. The Wallace patent describes methods for detecting cancer using an antibody labeled with fluorescein, phycolipoprotein, or tetraethyl rhodamine. The Hansen reference describes detection of hyman lymphocytes using tetrarhodamine isohiocyanate-labeled anti-IgG. Neither the Wallace patent nor the Hansen reference teaches or suggests that argininosuccinate synthetase levels in hepatoma or sarcoma cells of cancer patients should be measured to determine whether the patients are candidates for arginine deiminase therapy. Accordingly, for the reasons discussed above, the cited references, when considered individually or in combination, fail to teach or suggest methods for identifying cancer patients suffering from hepatoma or sarcoma who are susceptible to arginine deprivation therapy that involve determining the level of argininosuccinate synthetase protein present in hepatoma or sarcoma samples from the patients. Applicants accordingly, respectfully, request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. An early and favorable action is therefore respectfully requested.

Respectfully submitted,

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